IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Goldenberg

Serial No.: 10/002,211

Filed: December 5, 2001

Title: METHOD OF TREATING IMMUNE DISEASE USING B-CELL ANTIBODIES

Group Art Unit: 1644

Examiner: Chun Crowder

Attorney Docket No.: IMMU:003US1

EFS-WEB

DECLARATION UNDER 37 CFR §1.132

MAIL STOP AMENDMENT
COMMISSIONER FOR PATENTS
P.O. BOX 1450
ALEXANDRIA, VA 22313-1450

Sir:

I, Thomas Dörner, being duly warned, declare as follows:

1. I am a Professor of Medicine in the Department of Medicine/Rheumatology and Clinical Immunology, Charite Hospital, Berlin, Germany. I have an extensive background in autoimmune diseases and in the field of immunotherapy for the treatment of autoimmune diseases, as evidenced by my Curriculum Vitae, which is attached. In particular, I have been the principal investigator on clinical trials relating to immunotherapy of various autoimmune diseases with B-cell antibodies and TNF inhibitors. I have been the principal investigator of a study of the use of Immunomedics' antibody epratuzumab in systemic lupus erythematosus, for which Charite Hospital received grant funds. Dr. Goldenberg and I were co-authors on a paper publishing the results of this study ("Initial clinical trial of epratuzumab (humanized anti-CD22 antibody) for immunotherapy of systemic lupus erythematosus" *Arthritis Res Ther.* 2006;8(3):R74. Epub 2006 Apr 21), and Immunomedics covered a portion of my traveling expenses for presenting this paper at a scientific meeting. I have co-authored two other papers with Dr. Goldenberg (*Arthritis Rheum.* 2006 Jul;54(7):2344 and *Ann Rheum Dis.* 2007 Aug 2; [Epub ahead of print]). I have known Dr. Goldenberg of Immunomedics professionally for several years as a researcher in the field, and we interact at meetings and when we discuss

science. I have interacted with him twice when we attended scientific meetings in the past 3 years. I am being compensated on an hourly basis for my time in connection with this declaration.

2. I have read the Official Action dated July 26, 2007, for the above-captioned case. I have also reviewed the currently pending claims for this case and read the specification. I note in particular the following disclosures in the specification:

- "ablation of certain normal organs and tissues for other therapeutic purposes, such as the spleen in patients with immune disease or lymphomas, the bone marrow in patients requiring bone marrow transplantation, or normal cell types involved in pathological processes, such as certain T-lymphocytes in particular immune diseases" (page 7, lines 5-10)

- Another therapeutic application for such organ- and tissue-targeting antibodies conjugated with a toxic agent is for the ablation of certain normal cells and tissues as part of another therapeutic strategy, such as in bone marrow ablation with antibodies against bone marrow cells of particular stages of development and differentiation, and in the cytotoxic ablation of the spleen in patients with lymphoma or certain immune diseases, such as immune thrombocytopenic purpura, etc. (page 9, lines 2-10)

- "Specific examples include antibodies and fragments against bone marrow cells, particularly hematopoietic progenitor cells, pancreatic islet cells, spleen cells, parathyroid cells, uterine endometrium, ovary cells, testicular cells, thymus cells, B-cells, T-cells, Null cells, vascular endothelial cells, bile duct cells, gall bladder cells, prostate cells, hormone receptors such as of FSH, LH, TSH, growth factor receptors, such as of epidermal growth factor, urinary bladder cells, and vas deferens cells" (page 12, lines 12-20), and

- "Antibodies that target the spleen well include the LL2 (also known as EPB-2) monoclonal antibody, disclosed in Pawlak-Byczkowska, cancer Research, 49:4568-4577 (1989), which is directed against normal and

malignant B cells, and which can be used for treating normal spleen cells in patients with immune diseases, lymphoma, and other diseases" (page 12, lines 30-35).

3. I understand the examiner to say that the term "immune disease" would be unclear and ambiguous to a knowledgeable reader of the disclosure. In particular, the examiner states that this term might encompass disease in which the immune system is "positively (*e.g.*, autoimmune) or negatively (*e.g.*, HIV) regulated)." The terms "positively" versus "negatively" regulated have never been widely accepted by the scientific community, and current terminology, introduced in the early 2000s, refers to "disturbances in homeostasis of the immune system." There are a lot of otherwise defined diseases such as infections (HIV, other viruses, bacteria), malignant diseases (lymphoma), etc., which impair or affect the immune system. However, immune activation by all of these has a defined cause. By contrast, the classical term "immune disease," circa 1992, relates to **idiopathic** disorders of the immune system. These are the so-called classical autoimmune diseases for which the cause of immune activation was unknown.

4. As an immunologist and rheumatologist, and in the context of the entire disclosure of the above-identified application to include in particular those portions which I have identified above, I do not find this term to be unclear or ambiguous. I certainly would not understand the term to include disease in which the immune system is negatively regulated, such as HIV. The term is used in conjunction with a discussion of the use of a B-cell antibody and also in conjunction with a disclosure of the ablation of normal spleen cells and a disclosure of "certain immune diseases, such as immune thrombocytopenic purpura." In this regard, I immediately recognized that the reference in the disclosure of "antibodies that target the spleen," is a reference to a targeting of immune cells that reside in the spleen. B-cell hematologic abnormalities are a consequence of immune diseases in which the immune system is positively regulated, and immune thrombocytopenic purpura (ITP) is an example of such an immune disease. In particular, B cells differentiating into plasma cells are known to make antibodies, including the autoantibodies considered to be responsible for destroying platelets in ITP. Accordingly, I have no difficulty in ascertaining the scope of the term "immune disease" in the context of the present disclosure as referring to classical autoimmune diseases, and would not understand the term to include diseases such as HIV in which the immune system is "negatively regulated" (adopting, for the moment, the little-used and imprecise terminology employed in the Office Action). I therefore have no difficulty in determining the scope of the present claims.

5. Furthermore, after reading the specification of the above-identified application, I would understand that the applicant was in possession of a method of using B-cell antibodies generally to treat immune diseases, and not just the LL2 B-cell antibody specifically. The skilled artisan would understand that applicant's contribution to the art was the teaching that B cells generally could be used to treat immune diseases. The skilled artisan would not need to know the structure of particular B-cell antibodies in order to be apprised of the full scope of applicant's invention.

I hereby declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

11/28/2007
Date

T. Dörner, M.D.
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Curriculum vitae

Name:	Thomas **Dörner**, MD
Academic degrees:	Professor of Medicine
DOB:	October 20th, 1962
	Married with Marion E. Kamprath, Finance Director Europe, Holmesplace Ltd., Berlin
	1 daughter Marie (DOB September 26th, 1988)
email:	thomas.doerner@charite.de

Academic Graduation:

1990	Doctor of Medicine (summa cum laude) Charité, Humboldt-University Berlin
1998	Associate Professor of Medicine
2003	Professor of Medicine

Postdoctoral clinical training

1990-95	Internship and Residency of Internal Medicine, Charite Berlin, Board Certification as Doctor of Internal Medicine 1995 (Head: Prof. Dr. Gerd R. Burmester)
1991-2003	Member of the hemostaseology group under the leadership of the Institutes of transfusion and laboratory medicine at the Charite
1998-2000	Fellowship Rheumatology, Charite Berlin, Board Certification as rheumatologist 2000 (Head: Prof. Dr. Gerd R. Burmester)
1998-	Group Leader of the molecular immunology group at the Dept. of Medicine Charite/Rheumatology and Clinical Immunology
1998-99	Head of the Outpatients Dept. Dept. Med./Rheumatology Charite Berlin
1999-2003	Head of the Day care clinic/Dept. Rheumatology Charite Berlin
2001	Board certification for Transfusion Medicine, Immunology
2003	Head of the Division of Rheumatology/Dept. Medicine, Ludwigs Maximilian University Munich
Since 06/2004	Head of the interdisciplinary group Clinical Hemostaseology/Rheumatology & Head of the coagulation unit

Group leader "B cell memory" at the German Research Center of Rheumatology (DRFZ Berlin)

Research fellowships

1996-1998 Postdoctoral fellowship in clinical research in rheumatology and immunology, Department of Internal Medicine/Rheumatic Disease Division at the University of Texas, Southwestern Medical Center at Dallas, USA (Fellow of Peter E. Lipsky, MD)

Awards and honors

1990 Educational grant of the German Society of Rheumatology, Hannover

1993 Grant of the Deutsche Forschungsgemeinschaft to the 57th Meeting of the American College of Rheumatology, San Antonio, TX.

1998 "Senior Scholar Award" of the American College of Rheumatology, San Diego, CA.

2000 Rudolf-Schoen Award of the "Deutsche Gesellschaft für Rheumatologie"

2003 H-Schulze Award of the German League against Rheumatism

Journals

Member of the Editorial Board "Arthritis & Rheumatism"
Member of the Editorial Board of "Arthritis Research & Therapy"
Member of the Editorial Board "Rheumatology Reviews"
Member of the Editorial Board of Global Arthritis Research Network (GARN)

Congress Organization

International Symposiums "Rheumatology and Clinical Immunology" March 23rd –25th, 2000.
Annual Meeting of the German Association of Internists, rheumatological contributions since 2000, on behalf of the German Society of Rheumatology
Annual Meeting of the German Society of Rheumatology, 2002 in Berlin, Congress secretary
EULAR Meeting 2004, member of the international congress organization, Berlin, June 2004

Patents

Detection of anti-proteasome antibodies in body fluids (Patent Nr. 197 07 343.39).

Participation in clinical trials

- Ciprofloxacin long-term efficacy in reactive arthritis

- Randomised, placebo-controled study of the use of collagen II in early arthritis
- Randomised, placebo-controled study of the use of anakinra (IL1-Ra) in RA Arthritis
- Immune globuline therapy in systemic lupus erythematosus
- Oral pilocarpin (Salagen) in Sjögren's syndrome
- Cyclosporine A- tear drops in Sjögren's syndrome
- Immune adsorption (Prosorba) in SLE
- Immune adsorption in Sjögren's syndrome
- Epratuzumab (anti-CD22 antibody therapy) in SLE (PI)
- Epratuzumab in Sjögren's syndrome (PI)
- ADORE-study (etanercept monotherapy vs. MTX + Etanercept (Wyeth-Pharma) (PI)
- ASSERT-Study infliximab in ankylosing spondylitis (Centocor) (PI)
- COXA-study celecoxib vs. diclofenac (2 x 200 mg celecoxib vs. 2 x 75 diclofenac) Pharmacia/Pfizer (PI)
- DE 018 Open-label-Study D2E7 (Humira) in AS (Abbott-Pharmaceuticals) (PI)
- DE 013/D2E7 vs MTX vs. combination therapy (early RA) (Abbott) (PI)
- EDGE II-Studie etoricoxib vs diclofenac (gastrointestinal safety of etoricoxib) MSD (PI)
- Infliximab in ankylosing spondylitis (EU study for approval of IFX) Essex Pharma (PI)
- M02-497 D2E7-Study (Adalimumab) Abbott Wiesbaden (PI)
- RABBIT-study (long term comparison DMARDs vs. biologicals (PI)

Main research interests: Targeted therapy in rheumatic and inflammatory diseases and their impact on patient outcome and mechanism of action, B cell immunology, role of B cells and plasma cell subtypes in inflammatory rheumatic diseases, principles of the break of immune tolerance in autoimmunity, coagulation abnormalities in rheumatic diseases associated with enhanced cardiovascular risks.

Berlin, November 2007
Thomas Dörner, MD
Professor of Rheumatology & Hemostaseology